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(54) **Title:** IMPROVED STABILITY OF HYDROMORPHONE HYDROCHLORIDE SOLUTIONS

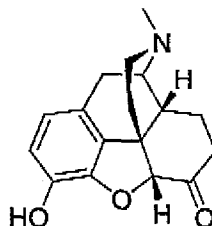
(57) **Abstract:** The present invention relates generally to a sterile hydromorphone hydrochloride solution that is substantially free of buffer.

## IMPROVED STABILITY OF HYDROMORPHONE HYDROCHLORIDE SOLUTIONS

[0001] This application claims the benefit of priority of United States provisional application No. 61/607,774, filed March 7, 2012, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[0002] The present invention relates generally to a sterile hydromorphone hydrochloride solution that is substantially free of buffer.

[0003] Hydromorphone hydrochloride (sold as Dilaudid, Laudicon, Hydromorphan) is a narcotic analgesic, and one of its principle uses is the relief of pain. It is a semi-synthetic  $\mu$ -opioid agonist. There is no intrinsic limit to the analgesic effect of hydromorphone hydrochloride; like morphine, adequate doses will relieve even the most severe pain. Hydromorphone is the generic (USAN) name (USP Dictionary of USAN and International Drug Names 2003) for 4,5- $\alpha$ -epoxy-3-hydroxy-17-methyl morphinan-6-one, a derivative of morphine. Its structural formula is:



Presently, intrathecal hydromorphone hydrochloride is commercially available for injection in 10 mg/ml solutions in a preservative-free formula containing 0.2% sodium citrate and 0.2% of a citric acid solution.

[0004] Hydromorphone is used in medicine as an alternative to morphine and diacetylmorphine for analgesia and as a second- or third-line narcotic antitussive (cough suppressant) for cases of dry, painful, paroxysmal coughing resulting from continuing bronchial irritation after influenza and other ailments, inhalation of fungus and other causes, and is generally regarded to be the strongest of the latter class of

drugs, and was developed shortly after another powerful antitussive, heroin, was removed from clinical use for this purpose in most of the world and in many countries banned outright.

[0005] The hydrogenation of morphine resulting in the formation of hydromorphone results in a drug with higher lipid solubility and ability to cross the blood-brain barrier and therefore more rapid and complete central nervous system penetration, with the result that hydromorphone is somewhat faster-acting and about eight times stronger than morphine and about three times stronger than heroin on a milligram basis. The effective morphine to hydromorphone conversion ratio can vary from patient to patient by a significant amount with relative levels of some liver enzymes being the main cause; the normal human range appears to be from 8:1 to a little under 4:1. It is not uncommon, for example, for the 8-mg tablet to have an effect similar to 30 mg of morphine sulfate or a similar morphine preparation.

[0006] The currently available hydromorphone hydrochloride solutions all contain buffer. The buffer is often added to a composition to regulate the pH and/or aid in the stability of the compound in solution. The addition of buffer can lead to potential complications such as toxicity, side effects and allergic responses. Further, the use of less or no buffer would decrease the costs of producing the pharmaceutical composition. Accordingly, there is a need for a hydromorphone hydrochloride solution that does not contain buffer. Surprisingly, it has been found that hydromorphone hydrochloride in water does not require buffering agents to maintain its stability over time.

[0007] Recently, there has been increasing interest in the regulation of the cerebrospinal fluid (CSF) pH. Part of this interest stems from the fact that the extracellular fluid (ECF) pH in the brain serves as an important regulator of pulmonary ventilation and a major determinant of cerebral blood flow. Furthermore, since the CSF pH has been shown to be subject to a considerable degree of homeostatic control in a variety of conditions which change the acid-base status of blood, many attempts have

been made to unravel the physiological mechanisms which are responsible for this control. Finally, since the acid-base metabolism of the cerebral compartments (including the ECF) may influence cerebral function to a significant degree, the CSF pH and the mechanisms which regulate it have become of concern to neurologists and neurosurgeons. CSF normally has a pH near 7.3. Since intrathecal delivery of hydromorphone hydrochloride is direct injection into the CSF, and it is desirable to keep the pH of the resulting CSF – hydromorphone solution mixture as close to 7.3 as possible, injection of a hydromorphone hydrochloride formulation with a pH near 7.3 is appealing. Indeed, the pH of the formulation without buffer is closer to the natural physiological pH of CSF than the formulation containing buffer (5.0 vs 4.1).

[0008] While there are no absolute FDA standards for sterilization processes, pharmaceutical solutions are most commonly sterilized using a heating regimen at 121.1°C with an  $F_0$  of about 30 minutes. While this may be an effective method for thermally stable compounds, this practice is counterproductive for some heat-labile active pharmaceutical ingredients (API's). In these cases, the resulting solution may be sterile, but it is often plagued with an unacceptable increase in degradation products brought on by the excessive use of heat in the sterilization process. Furthermore, compositions containing heat-labile API's are often not terminally sterilized to avoid this degradation. Therefore, it is desirable to find and implement a sterilization method that utilizes less harsh conditions in order to prevent this thermal degradation from taking place, while continuing to meet sterility standards.

[0009] Indeed, during the terminal sterilization process, heat-labile hydromorphone undergoes transformations to undesirable side products such as hydromorphone N-oxide (HNO), 6- $\beta$ -tetrahydrooripavine (THO), dihydromorphone (DHM), and pseudo-hydromorphone (PHM). This obviously reduces the amount of hydromorphone in solution, and thus the overall efficacy of the solution. Additionally, this degradation product may have undesirable side effects, including toxicity. The amount of side products found in commercially available hydromorphone solutions is shown in the table below.

| Hydromorphone Hydrochloride (Commercial) |       |       |       |
|--|-------|-------|-------|
| 10 mg/mL                                 |       |       |       |
| % HNO                                    | % THO | %DHM  | % PHM |
| <0.05                                    | <0.05 | <0.05 | 0.5   |

[0010] An alternative to terminal sterilization is aseptic processing, which is the process by which a sterile (aseptic) product is packaged in a sterile container in a way which maintains sterility. This avoids the harsh conditions of terminal sterilization without sacrificing sterility of the resulting solution. It was hypothesized that aseptic processing may lead to a solution with fewer degradation products, as the hydromorphone would not be subjected to the rigors of the terminal sterilization process.

[0011] Therefore, there is a clinical need for aqueous solutions of hydromorphone having fewer degradation products, preferably for concentrated solutions that are also stable in a variety of storage conditions for extended periods of time. Due to the heat-lability of the hydromorphone product, aseptic processing is herein disclosed for the reduction of impurities in the hydromorphone solution.

[0012] Disclosed herein is a pharmaceutical composition comprising a sterile, intrathecal, aqueous hydromorphone hydrochloride solution, wherein said composition is substantially free of buffer.

[0013] In an embodiment, a solution of intrathecal hydromorphone hydrochloride contains less than 1.0% pseudo-hydromorphone.

[0014] According to a further aspect, a solution of intrathecal hydromorphone hydrochloride contains less than 0.1% pseudo-hydromorphone.

[0015] In an embodiment, a solution of intrathecal hydromorphone hydrochloride contains less than 0.2% hydromorphone N-oxide.

[0016] According to another aspect, a solution of intrathecal hydromorphone hydrochloride is substantially free of hydromorphone N-oxide.

[0017] According to another aspect, a solution of intrathecal hydromorphone hydrochloride is substantially free of dihydromorphone.

[0018] According to another aspect, a solution of intrathecal hydromorphone hydrochloride is substantially free of 6- $\beta$ -tetrahydrooripavine.

[0019] According to one embodiment, the solution described herein is not terminally sterilized.

[0020] According to another aspect, the solution described herein is free of particulates.

[0021] According to yet another aspect, the solution described herein is stable at 25°C and 60% relative humidity for at least 1 month.

[0022] According to yet another aspect, the solution described herein is stable at 30°C and 65% relative humidity for at least 1 month.

[0023] According to a further aspect, the solution described herein is stable at 40°C and 75% relative humidity for at least 1 month.

[0024] According to yet another aspect, the solution described herein is stable at 25°C and 60% relative humidity for at least 3 months.

[0025] According to yet another aspect, the solution described herein is stable at 30°C and 65% relative humidity for at least 3 months.

[0026] According to a further aspect, the solution described herein is stable at 40°C and 75% relative humidity for at least 3 months.

[0027] According to yet another aspect, the solution described herein is stable at 25°C and 60% relative humidity for at least 6 months.

[0028] According to yet another aspect, the solution described herein is stable at 30°C and 65% relative humidity for at least 6 months.

[0029] According to a further aspect, the solution described herein is stable at 40°C and 75% relative humidity for at least 6 months.

[0030] According to yet another aspect, the solution described herein is stable at 25°C and 60% relative humidity for at least 1 year.

[0031] According to yet another aspect, the solution described herein is stable at 30°C and 65% relative humidity for at least 1 year.

[0032] According to a further aspect, the solution described herein is stable at 40°C and 75% relative humidity for at least 1 year.

[0033] According to yet another aspect, the solution described herein is stable at 25°C and 60% relative humidity for at least 2 years.

[0034] According to yet another aspect, the solution described herein is stable at 30°C and 65% relative humidity for at least 2 years.

[0035] According to a further aspect, the solution described herein is stable at 40°C and 75% relative humidity for at least 2 years.

[0036] According to another aspect, the solution described herein is suitable for intrathecal delivery.

[0037] Disclosed herein is a pharmaceutical composition consisting of a sterile, aqueous solution of hydromorphone hydrochloride.

[0038] In an embodiment, the concentration of the hydromorphone hydrochloride solution is 10.0 mg/mL.

[0039] In an embodiment, the concentration of the hydromorphone hydrochloride solution is 2.0 mg/mL.

[0040] Disclosed herein is a method of treating pain by administration of a composition comprising a sterile aqueous solution of hydromorphone hydrochloride, wherein said composition is substantially free of buffer.

[0041] Disclosed herein is a composition comprising a sterile aqueous solution of hydromorphone hydrochloride for use in human therapy, wherein said composition is substantially free of buffer.

[0042] Disclosed herein is the use of a sterile aqueous solution of hydromorphone hydrochloride in human therapy, wherein said composition is substantially free of buffer.

[0043] Disclosed herein is a composition comprising a sterile aqueous solution of hydromorphone hydrochloride for use in treating pain, wherein said composition is substantially free of buffer.



[0044] Disclosed herein is the use of a composition comprising a sterile aqueous solution of hydromorphone hydrochloride for use in treating pain, wherein said composition is substantially free of buffer.

[0045] Disclosed herein is the use of a composition comprising a sterile aqueous solution of hydromorphone hydrochloride for the manufacture of a medicament to treat pain, wherein said composition is substantially free of buffer.

[0046] As used herein, the terms below have the meanings indicated.

[0047] The term “about,” as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term “about” should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[0048] The term “sterile,” as used herein, means free from all live bacteria or other microorganisms and their spores.

[0049] The term “particulate,” as used herein, is meant to describe mobile undissolved particles, other than gas bubbles, unintentionally present in the drug solution.

[0050] The term “intrathecal,” as used herein, means introduced into or occurring in the space under the arachnoid membrane which covers the brain and spinal cord. Intrathecal drug delivery is designed to manage chronic pain and/or spasticity, such as intractable cancer pain, by delivering pain medication directly to the intrathecal space. Intrathecal drug delivery uses an implantable infusion system to deliver pain medication directly to the intrathecal space via a surgically implanted infusion pump and catheter.

[0051] The term “stable” as used herein in reference to claimed compositions means retaining substantially the same properties and characteristics throughout its period of storage and use that it possessed at the time of its manufacture, such that the composition provides substantially the same therapeutic benefit to the patient over the period of time that the composition is stored and delivered, such as for 1 month, 3 months, 6 months, 1 year, or 2 years. The compositions disclosed herein are stable if they contain within 3% of the amount of hydromorphone hydrochloride as claimed on the label (%LC) after 12 weeks, as determined by HPLC assay.

[0052] Certain embodiments disclosed herein may be illustrated by the following non-limiting examples.

#### Example 1

##### **Preparation of 10.0 mg/mL hydromorphone hydrochloride solution with 0.2% citrate buffer**

To 1 L of water for injection (WFI) is added 40.4 g citrate buffer, and the mixture is stirred for  $10 \pm 2$  minutes. To the resulting solution is added 200.0 g hydromorphone hydrochloride and 2 L WFI. The mixture is then stirred for 45 minutes. The resulting solution is diluted to 20 L with WFI and stirred for at least an additional 10 minutes.

#### Example 2

##### **Preparation of 10.0 mg/mL hydromorphone hydrochloride solution with 0.1% citrate buffer**

To 1 L of WFI is added 20.2 g citrate buffer, and the mixture is stirred for  $10 \pm 2$  minutes. To the resulting solution is added 200.0 g hydromorphone hydrochloride and 2 L WFI. The mixture is then stirred for 45 minutes. The resulting solution is diluted to 20 L with WFI and stirred for at least an additional 10 minutes.

#### Example 3

**Preparation of 10.0 mg/mL hydromorphone hydrochloride solution with 0.05% citrate buffer**

To 1 L of WFI is added 10.1 g citrate buffer, and the mixture is stirred for  $10 \pm 2$  minutes. To the resulting solution is added 200.0 g hydromorphone hydrochloride and 2 L WFI. The mixture is then stirred for 45 minutes. The resulting solution is diluted to 20 L with WFI and stirred for at least an additional 10 minutes.

Example 4

**Preparation of 10.0 mg/mL hydromorphone hydrochloride solution with 0.03% citrate buffer**

To 1 L of WFI is added 6.06 g citrate buffer, and the mixture is stirred for  $10 \pm 2$  minutes. To the resulting solution is added 200.0 g hydromorphone hydrochloride and 2 L WFI. The mixture is then stirred for 45 minutes. The resulting solution is diluted to 20 L with WFI and stirred for at least an additional 10 minutes.

Example 5

**Preparation of 10.0 mg/mL hydromorphone hydrochloride solution with 0% citrate buffer**

To 3 L of WFI is added 200.0 g hydromorphone hydrochloride. The mixture is stirred for 45 minutes. The resulting solution is diluted to 20 L with WFI and stirred for at least an additional 10 minutes.

Example 6

**Impurity profile of hydromorphone hydrochloride solutions with varying amounts of buffer**

The impurity profile of Examples 1-5, showing the amount of each impurity, as well as the percent of the label claim (%LC) of the API, as determined by HPLC assay.

|                                    |
|------------------------------------|
| <b>Buffer-containing Solutions</b> |
|------------------------------------|

| % Buffer | pH  | %L.C. | %HMN  | %DHM  | %THO  | %0.56 RRT | %Pseudo-HM |
|----------|-----|-------|-------|-------|-------|-----------|------------|
| 0        | 5.0 | 99.0  | <0.05 | <0.05 | <0.05 | <0.05     | <0.05      |
| 0.03     | 4.2 | 100.4 | <0.05 | <0.05 | <0.05 | <0.05     | <0.05      |
| 0.05     | 4.1 | 101.1 | <0.05 | <0.05 | <0.05 | <0.05     | <0.05      |
| 0.1      | 4.1 | 100.7 | <0.05 | <0.05 | <0.05 | <0.05     | 0.05       |
| 0.2      | 4.1 | 100.1 | <0.05 | <0.05 | <0.05 | <0.05     | <0.05      |

#### Example 7

#### **Impurity profile of hydromorphone hydrochloride solution with 0% buffer over time**

The impurity profile of Example 5 over time, showing the amount of each impurity, as well as the percent of the label claim (%LC) of the API, as determined by HPLC assay.

| Time (Days) | pH  | %L.C. | %HMN  | %DHM  | %THO  | %Pseudo-HM |
|-------------|-----|-------|-------|-------|-------|------------|
| 0           | 5.0 | 99.0  | <0.05 | <0.05 | <0.05 | <0.05      |
| 3           | -   | 97.7  | <0.05 | <0.05 | <0.05 | <0.05      |
| 7           | -   | 99.7  | <0.05 | <0.05 | <0.05 | <0.05      |
| 14          | 4.6 | 102.4 | <0.05 | <0.05 | <0.05 | 0.06       |
| 28          | 4.6 | 99.3  | <0.05 | <0.05 | <0.05 | 0.07       |
| 56          | 4.6 | 99.0  | <0.05 | <0.05 | <0.05 | 0.07       |
| 84          | 4.5 | 100.5 | <0.05 | <0.05 | <0.05 | 0.09       |

[0053] The data shows that compositions containing buffer have the same levels of impurities as the composition without buffer. This indicates that the buffer is not an essential part of the composition from an impurity standpoint. Further, additional data shows that the buffer-free composition maintains its low levels of impurities over time, indicating that buffer is not essential to the long-term stability of the composition.

[0054] The formulation without buffer has a small pH change (only 0.5 pH units) over the time period tested. This indicates that the buffer is not necessary to keep the pH stable over time. This pH data, coupled with the impurity data, shows that the small

change in pH that is observed does not have a detrimental effect on the purity of the formulation. Further, the absence of the buffer gives the formulation a pH closer to the patient's natural physiological pH of the cerebrospinal fluid than the formulation containing the buffer (5.0 vs. 4.1).

[0055] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

***What is Claimed is:***

1. A pharmaceutical composition comprising a sterile aqueous solution of hydromorphone hydrochloride, wherein said composition is substantially free of buffer.
2. The composition as recited in claim 1, wherein said composition contains less than 1.0% pseudo-hydromorphone.
3. The composition as recited in claim 2, wherein said composition contains less than 0.1% pseudo-hydromorphone.
4. The composition as recited in claim 1, wherein said composition contains less than 0.2% hydromorphone N-oxide.
5. The composition as recited in claim 4, wherein said composition is substantially free of hydromorphone N-oxide.
6. The composition as recited in claim 1, wherein said composition is substantially free of dihydromorphone.
7. The composition as recited in claim 1, wherein said composition is substantially free of 6- $\beta$ -tetrahydrooripavine.
8. The composition as recited in claim 1, wherein said composition is substantially free of particulates.
9. The composition as recited in claim 1, wherein said composition is suitable for intrathecal delivery.
10. The composition as recited in claim 1, wherein said composition is stable at 25°C and 60% relative humidity for at least 3 months.
11. The composition as recited in claim 1, wherein said composition is stable at 30°C and 65% relative humidity for at least 3 months.
12. The composition as recited in claim 1, wherein said composition is stable at 40°C and 75% relative humidity for at least 3 months.
13. The composition as recited in claim 1, wherein said composition is not terminally sterilized.
14. The composition as recited in claim 1, having a liquid drug formulation wherein the concentration of hydromorphone hydrochloride is about 10.0 mg/mL.

15. The composition as recited in claim 1, having a liquid drug formulation wherein the concentration of hydromorphone hydrochloride is about 2.0 mg/mL.
16. A pharmaceutical composition consisting essentially of a sterile aqueous solution of hydromorphone hydrochloride.

**INTERNATIONAL SEARCH REPORT**

International application No  
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**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61K9/00 A61K31/485  
 ADD.  
 According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 A61K  
 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

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Authorized officer  
 Kling, Isabelle



# INTERNATIONAL SEARCH REPORT

Information on patent family members

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